

NDA 18-723/S-028  
NDA 19-680/S-014  
NDA 20-593/S-002  
NDA 18-081/S-032  
NDA 18-082/S-023

JUN 19 2000

Abbott Laboratories  
Attention: James D. Steck  
Director, PPD Regulatory Affairs  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

Dear Mr. Steck:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote Tablets (divalproex sodium delayed release tablets), Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules), Depacon Injection (valproate sodium injection), Depakene Capsules (valproic acid capsules, USP), and Depakene Syrup (valproic acid syrup, USP).

	<u>Initial Submission</u>	<u>Response to Action Letter</u>	<u>Additional Amendment</u>
NDA 18-723/S-028	June 15,1999	February 23,2000	April 5,2000
NDA 19-680/S-014	September 13,1999	April 5,2000	
NDA 20-593/S-002	September 13, 1999	April 5,2000	
NDA 18-081/S-032	September 13,1999	May 26,2000	
NDA 18-082/S-023	September 13,1999	May 26,2000	

These "Changes Being Effected" supplemental new drug applications provide for addition of the following new safety information to the labeling of these products:

1. Statements in the PRECAUTIONS and ADVERSE REACTIONS sections of labeling regarding a valproate/amitriptyline/nortriptyline drug interaction, anaphylaxis, parkinsonism, and effects of valproate on HIV replication.
2. Information in the WARNINGS section and in the Geriatric subsection of the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of labeling regarding somnolence in the elderly.
3. Statements in the Box Warning and WARNINGS section of labeling regarding pancreatitis.

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We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Please note that the following revisions have been made to labeling since your last submissions:

1. The word “a” has been deleted from the 1<sup>st</sup> sentence in the 2<sup>nd</sup> paragraph of the CLINICAL TRIALS/Epilepsy section in the Depakote Tablet, Depakote Sprinkle Capsules, and Depakene Capsule and Syrup package inserts.
2. The word “vasodilation” has been added to the ADVERSE REACTIONS/Mania/Cardiovascular section in the Depacon package insert.
3. The “Pediatric” and “Geriatric” subheaders in the PRECAUTIONS section have been revised to “Pediatric Use” and “Geriatric Use” in all four package inserts.
4. The word “an” has been added to the last sentence (in front of “increase”) of the Mutagenicity subsection in the PRECAUTIONS section in the Depakote Tablet, Depakote Sprinkle Capsules, and Depakene Capsule and Syrup package inserts.
5. The 2<sup>nd</sup> sentence of the 1<sup>st</sup> paragraph of the DOSAGE AND ADMINISTRATION/Epilepsy section has been replaced with the following sentence, “DEPAKOTE is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures.” in the Depakote Tablet and Depakote Sprinkle Capsules package inserts.
6. The reference to (15-25°F) has been corrected to (15-25°C) in the HOW SUPPLIED section in the Depakene Capsule and Syrup package insert.
7. The word “children” has been changed to “pediatric patients” in the 1<sup>st</sup> sentence of the 1<sup>st</sup> paragraph of the PRECAUTIONS/Pediatric section in the Depacon package insert.

Lastly, several minor punctuation and spelling errors have been corrected.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

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Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 18-723/S-028, 19-680/S-014, 20-593/S-002, 18-081/S-032, 18-082/S-023." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please note that we have reviewed the content of the following supplements submitted as "changes being effected," and we note that these changes have been incorporated in the enclosed labeling text. Therefore, the supplemental applications listed below have been superceded, and will be retained in our files with no further action.

<u>Supplement Number:</u>	<u>Date Submitted:</u>
NDA 18-723/S-023	February 26, 1997
NDA 19-680/S-012	February 26, 1994

We remind you that the Dear Health Care Professional letter is to be mailed utilizing the "Important Drug Warning" statement and red rectangular border as described under 21 CFR 200.5. We also ask that you consider utilizing this statement (and its border) on the first page of the Dear Health Care Professional letter in the upper right hand corner.

Additionally, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

**DEPAKENE®**  
**VALPROIC ACID**  
**CAPSULES AND SYRUP**  
**R<sub>x</sub> only**

**BOX WARNING:**

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

**TERATOGENICITY:**

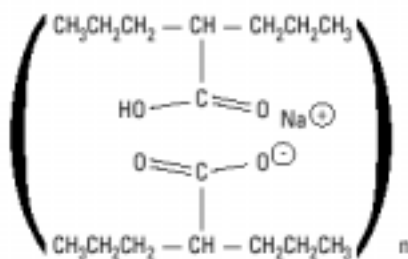
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA), ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS

**PANCREATITIS:**

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See WARNINGS and PRECAUTIONS.)

**DESCRIPTION**

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Valproic acid has the following structure:



Valproic acid (pKa 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/mL) and very soluble in organic solvents.

DEPAKENE capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt.

#### Inactive Ingredients

250 mg capsules: corn oil, FD&C Yellow No. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide.

Syrup: FD&C Red No. 40, glycerin, methylparaben, propylparaben, sorbitol, sucrose, water, and natural and artificial flavors.

### CLINICAL PHARMACOLOGY

#### Pharmacodynamics

Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

#### Absorption/Bioavailability

Equivalent oral doses of DEPAKOTE (divalproex sodium) products and DEPAKENE (valproic acid) capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in  $T_{\max}$  and  $C_{\max}$  could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the DEPAKOTE tablet (increase in  $T_{\max}$  from 4 to 8 hours) than on the absorption of the DEPAKOTE sprinkle capsules (increase in  $T_{\max}$  from 3.3 to 4.8 hours).

While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Co-administration of oral valproate products with food and substitution among the various DEPAKOTE and DEPAKENE formulations should cause no clinical problems in the management of patients with epilepsy (see **DOSAGE AND ADMINISTRATION**). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

#### Distribution

##### Protein Binding:

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40  $\mu\text{g/mL}$  to 18.5% at 130  $\mu\text{g/mL}$ . Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See **PRECAUTIONS, Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

#### CNS Distribution:

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

#### Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial  $\beta$ -oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

#### Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m<sup>2</sup> and 11 L/1.73 m<sup>2</sup>, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m<sup>2</sup> and 92 L/1.73 m<sup>2</sup>. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

#### Special Populations

##### Effect of Age:

Neonates - Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children - Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly - The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See **DOSAGE AND ADMINISTRATION**).

##### Effect of Gender:

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m<sup>2</sup>, respectively).

##### Effect of Race:

The effects of race on the kinetics of valproate have not been studied.

##### Effect of Disease:

Liver Disease - (See **BOXED WARNING, CONTRAINDICATIONS, and WARNINGS**). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease - A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%.

Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is sub-stantially reduced; thus, monitoring total concentrations may be misleading.

### Plasma Levels and Clinical Effect

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 µg/mL to 18.5% at 130 µg/mL. Higher than expected free fractions occur in the elderly, in hyper-lipidemic patients, and in patients with hepatic and renal diseases.

### Epilepsy:

The therapeutic range in epilepsy is commonly considered to be 50 to 100 µg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

### Clinical Trials

The studies described in the following section were conducted using DEPAKOTE (divalproex sodium) tablets.

### Epilepsy

The efficacy of DEPAKOTE in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

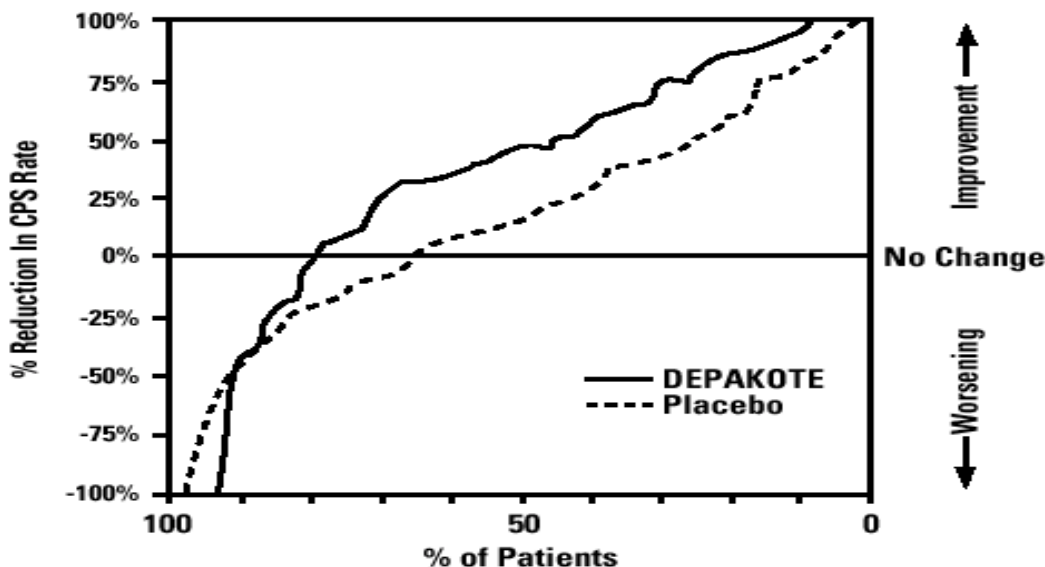
In one, a multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

Adjunctive Therapy Study Median Incidence of CPS per 8 Weeks			
Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

\*Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at  $p \leq 0.05$  level.

Figure 1 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a  $\geq 50\%$  reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

**Figure 1**



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 µg/mL in the low dose and high dose groups, respectively.

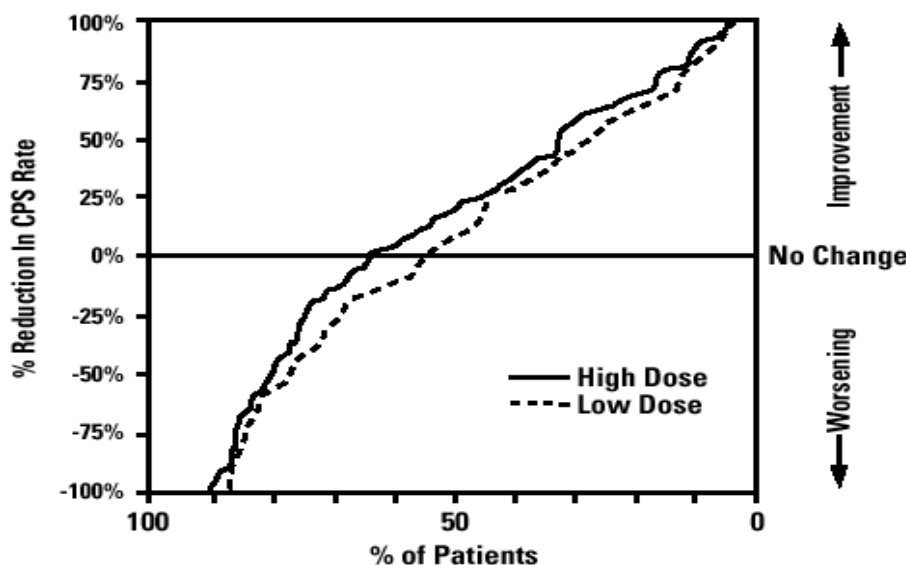
The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

<b>Monotherapy Study</b> <b>Median Incidence of CPS per 8 Weeks</b>			
<b>Treatment</b>	<b>Number of Patients</b>	<b>Baseline Incidence</b>	<b>Randomized Phase Incidence</b>
High dose DEPAKOTE	131	13.2	10.7*
Low dose DEPAKOTE	134	14.2	13.8

\* Reduction from baseline statistically significantly greater for high dose than low dose at  $p \leq 0.05$  level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose DEPAKOTE.

**Figure 2**



## INDICATIONS AND USAGE

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures.



Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE **WARNINGS** FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

## **CONTRAINDICATIONS**

VALPROIC ACID SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

Valproic acid is contraindicated in patients with known hypersensitivity to the drug.

## **WARNINGS :**

### **Hepatotoxicity**

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering DEPAKOTE products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

### **Pancreatitis**

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see **BOXED WARNING**).

### **Somnolence in the Elderly**

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**).

### **Thrombocytopenia**

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see **PRECAUTIONS**]) may be dose-related. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets  $\leq 75 \times 10^9/L$ . Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts

normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of  $\geq 110$   $\mu\text{g/mL}$  (females) or  $\geq 135$   $\mu\text{g/mL}$  (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

### **Usage In Pregnancy**

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARA-METHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230  $\mu\text{g/mL}$  (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a  $\text{mg/m}^2$  basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340  $\mu\text{g/mL}$  or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a  $\text{mg/m}^2$  basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a  $\text{mg/m}^2$  basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280  $\mu\text{g/mL}$  (2.8 times the upper limit of the human therapeutic range).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

## **PRECAUTIONS**

### **Hepatic Dysfunction**

See **BOXED WARNING**, **CONTRAINDICATIONS** and **WARNINGS**.

### **Pancreatitis**

See **BOXED WARNING**, and **WARNINGS**

### **General**

Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKENE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets  $\leq 75 \times 10^9/L$ . Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of  $\geq 110 \mu g/mL$  (females) or  $\geq 135 \mu g/mL$  (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPAKENE therapy should be modified or discontinued.

Since DEPAKENE may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See **PRECAUTIONS-Drug Interactions**.)

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

There are *in vitro* studies which suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

### **Information for Patients**

Since DEPAKOTE products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

### **Drug Interactions**

#### Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

#### Drugs for which a potentially important interaction has been observed:

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction

was increased 4-fold in the presence of aspirin compared to valproate alone. The B-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

**Felbamate** - A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 ug/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 gg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

**Rifampin** - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

#### Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

**Antacids** - A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

**Chlorpromazine** - A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

**Haloperidol** - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

**Cimetidine and Ranitidine** - Cimetidine and ranitidine do not affect the clearance of valproate.

#### Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydase, and glucuronyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

#### Drugs for which a potentially important valproate interaction has been observed:

**Amitriptyline/Nortriptyline** - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

**Carbamazepine/carbamazepine- 10,11 -Epoxide** - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon coadministration of valproate and CBZ to epileptic patients.

**Clonazepam** - The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

**Diazepam** - Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

**Ethosuximide** - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15%

decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

**Lamotrigine** - In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate.

**Phenobarbital** - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum

concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate. Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin - Valproate displaces phenytoin from its plasma albumin bindingsites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin - In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if DEPAKENE therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Acetaminophen - Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine - In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium - Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam - Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids - Administration of a single-dose of ethinylloestradiol (50 ug)/levonorgestrel (250 ug) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### **Carcinogenesis**

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m<sup>2</sup> basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

### **Mutagenesis**

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of increase in SCE frequency is not known.

### **Fertility**

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m<sup>2</sup> basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m<sup>2</sup> basis). Segment I fertility studies in rats have shown doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m<sup>2</sup> basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

### **Pregnancy**

Pregnancy Category D: See **WARNINGS**.

### **Nursing Mothers**

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when divalproex sodium is administered to a nursing woman.

### **Pediatric Use**

Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see **BOXED WARNING**). When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a  $\text{mg}/\text{m}^2$  basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a  $\text{mg}/\text{m}^2$  basis.

### **Geriatric Use**

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see **WARNINGS-Somnolence in the Elderly**). The starting dose should be reduced in these patients, and dosage reductions or discontinuation for somnolence (see **DOSAGE AND ADMINISTRATION**).

## **ADVERSE REACTIONS**

### **Epilepsy**

The data described in the following section were obtained using DEPAKOTE (divalproex sodium) tablets.

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 1 lists treatment-emergent adverse events which were reported by  $\geq 5\%$  of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

**Table 1**  
**Adverse Events Reported by  $\geq 5\%$  of Patients Treated**  
**with DEPAKOTE During Placebo-Controlled Trial of**  
**Adjunctive Therapy for Complex Partial Seizures**

<b>Body System/Event</b>	<b>Depakote (%)</b> <b>(n = 77)</b>	<b>Placebo (%)</b> <b>(n = 70)</b>
<b>Body as a Whole</b>		
Headache	31	21
Asthenia	27	7
Fever	6	4
<b>Gastrointestinal System</b>		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
<b>Nervous System</b>		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
<b>Respiratory System</b>		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
<b>Other</b>		
Alopecia	6	1
Weight Loss	6	0

Table 2 lists treatment-emergent adverse events which were reported by  $\geq 5\%$  of patients in the high dose DEPAKOTE group, and for which the incidence was greater than in the low dose group, in a controlled trial of DEPAKOTE monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

**Table 2**  
**Adverse Events Reported by  $\geq 5\%$  of Patients in the High Dose Group in the Controlled Trial of DEPAKOTE Monotherapy for Complex Partial Seizures<sup>1</sup>**

<b>Body System/Event</b>	<b>High Dose (%) (n = 131)</b>	<b>Low Dose (%) (n = 134)</b>
<b>Body as a Whole</b>		
Asthenia	21	10
<b>Digestive System</b>		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
<b>Hemic/Lymphatic System</b>		
Thrombocytopenia	24	1
Ecchymosis	5	4
<b>Metabolic/Nutritional</b>		
Weight Gain	9	4
Peripheral Edema	8	3
<b>Nervous System</b>		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
<b>Respiratory System</b>		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
<b>Skin and Appendages</b>		
Alopecia	24	13
<b>Special Senses</b>		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

<sup>1</sup> Headache was the only adverse event that occurred in  $\geq 5\%$  of patients in the high dose group and at an equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with DEPAKOTE in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.

Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.

Skin and Appendages: Rash, pruritus, dry skin.

Special Senses: Taste perversion, abnormal vision, deafness, otitis media.

Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.



### Other Patient Populations

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

**Gastrointestinal:** The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

**CNS Effects:** Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

**Dermatologic:** Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and had with a history of multiple cutaneous drug reactions.

**Psychiatric:** Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

**Musculoskeletal:** Weakness.

**Hematologic:** Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General and Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

**Hepatic:** Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see **WARNINGS**).

**Endocrine:** Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

**Pancreatic:** Acute pancreatitis including fatalities.

**Metabolic:** Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

**Genitourinary:** Enuresis and urinary tract infection.

**Special Senses:** Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

**Other:** Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

### Mania

Although DEPAKENE has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE tablets.

**Body as a Whole:** Chills, neck pain, neck rigidity.

**Cardiovascular System:** Hypotension, postural hypotension.

**Digestive System:** Fecal incontinence, gastroenteritis, glossitis.

**Musculoskeletal System:** Arthrosis.

**Nervous System:** Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

**Skin and Appendages:** Furunculosis, maculopapular rash, seborrhea.

Special Senses: Conjunctivitis, dry eyes, eye pain.

Urogenital System: Dysuria.

### **Migraine**

Although DEPAKENE has not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE tablets.

Body as a Whole: Face edema.

Digestive System: Dry mouth, stomatitis.

Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

### **OVERDOSAGE**

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 µg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

### **DOSAGE AND ADMINISTRATION**

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

DEPAKENE (valproic acid) is administered orally. DEPAKENE is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the DEPAKENE dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see **PRECAUTIONS - Drug Interactions**).

Complex Partial Seizures: For adults and children 10 years of age or older.

Monotherapy (Initial Therapy): DEPAKENE has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 µg/mL in females and 135 µg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 - 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of DEPAKENE therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy: DEPAKENE may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE, no adjustment of carbamazepine or phenytoin dosage was needed (see **CLINICAL STUDIES**). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see **Drug Interactions**), periodic plasma concentration determinations of concomitant AEDs are recommended during

the early course of therapy (see **PRECAUTIONS - Drug Interactions**). Simple and Complex Absence Seizures: The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 ug/mL. Some patients may be controlled with lower or higher serum concentrations (see **CLINICAL PHARMACOLOGY**).

As the DEPAKENE dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see **PRECAUTIONS**).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup		
(Kg)	(Lb)		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	0	0	1
25-39.9	55-87.9	500	1	0	1
40-59.9	88-131.9	750	1	1	1
60-74.9	132-164.9	1,000	1	1	2
75-89.9	165-197.9	1,250	2	1	2

### General Dosing Advice

**Dosing in Elderly Patients** - Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced. Dosages should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see **WARNINGS**).

**Dose-Related Adverse Events** - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of  $\geq 110 \mu\text{g/mL}$  (females) or  $\geq 135 \mu\text{g/mL}$  (males) (see **PRECAUTIONS**). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

**G.I. Irritation** - Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

### HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid, bearing the trademark DEPAKENE for product identification, in bottles of 100 capsules (NDC 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 mL as the sodium salt in bottles of 16 ounces (NDC 0074-5682-16). Store capsules at 59-77°F (15-25°C). Store syrup below 86°F (30°C).



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